her rejections of claims 1-4, 10-12 and 14-17 under 35 USC § 103(a) over Gulbrandsen et al. ('790).

Summary Of The Prosecution To Date

The Examiner has taken the position that the cited references teach a generic group of vitamin D derivatives that includes applicants' claimed vitamin D5 compounds. Applicants did not contest this position. However, in rebuttal, applicants submitted the Declaration of Dr. Robert Moriarty as evidence that 1α(OH)D5 possesses a key property (significantly lower calcemic activity compared to the closest prior art compounds) that would have been unexpected to a person of ordinary skill in the art at the time of the invention. The Examiner contended that this lower calcemic activity is not unexpected in view of evidence in the prior art that the claimed compounds act as antiproliferative agents and cell differentiating agents without significantly altering calcium metabolism. The Examiner maintains her rejections on this basis.

The Teachings Of The Prior Art

The sole evidence offered by the Examiner that the prior art teaches that the claimed vitamin D5 compounds would be expected to have lower calcemic activity is Bishop U.S. Patent No. 5,763,429 at col. 5, line 60 to col. 6, line 13. There Bishop states that "[t]he 1α-hydroxyvitamin D compounds of formula I of the present invention are those that ... have a lower tendency or inability to cause hypercalcemia and/or hypercalcuria [than the

vitamin D3 compounds]." A person skilled in the art would not have interpreted this statement to mean that all 1α-hydroxyvitamin D compounds have a lower tendency or inability to cause hypercalcemia and/or hypercalcuria than the vitamin D3 compounds. Bishop provides no data to support such an interpretation and gives no reason why it should be so. A more reasonable interpretation of Bishop is that Bishop is saying the 1α-hydroxyvitamin D compounds of formula I that enable the invention are those that have a lower tendency or inability to cause hypercalcemia and/or hypercalcuria.

Even if Bishop intended to teach that all 1α-hydroxyvitamin D compounds have a lower tendency or inability to cause hypercalcemia and/or hypercalcuria than the vitamin D3 compounds, Knutson et al. Patent No. 5,488,120 and its file history clearly teach that this is not true by presenting data showing that 1α(OH)D4 has essentially the same effect on serum calcium as 1α(OH)D_3 and 1α,25(OH)$_2$D3.

Significantly, Bishop cites the Knutson '120 patent as teaching a means for synthesizing compounds of formula I having low calcemic activity (Bishop et al. col. 6, lines 41-41), yet, as explained above, Knutson teaches that 1α(OH)D4 has high calcemic activity. Clearly, Bishop did not mean to teach that all 1α-hydroxyvitamin D compounds are low in calcemic activity since he knew of Knutson's patent and its teaching that 1α(OH)D4 is effective at increasing serum calcium (Knutson et al. col. 6,

lines 29-31).

Knutson Teaches That 1α(OH)D4 And 1α(OH)D3 Have Essentially The Same Calcemic Activity

In the Final Office Action, the Examiner noted that the closest prior art compounds are the vitamin D4 compounds. These vitamin D4 compounds, and 1α(OH)D_4 in particular, are the subject of Knutson et al. Patent No. 5,488,120, disclosed by applicants during the parent case. In developing 1α(OH)D4, Dr. Knutson and her colleagues were searching for a vitamin D compound of low toxicity that could be used as a therapeutic agent (col. 2, lines 9-11). In other words, they were searching for a compound that had essentially the same high calcium retaining ability as vitamin D3 but with lower toxicity. The compound they selected was 1α(OH)D4. Knutson teaches that 1α(OH)D4 "compares favorably to" 1α,25(OH)2D3 in increasing serum calcium level in vitamin D deficient rats (col. 6, lines 29-30).

During the prosecution of the vitamin D4 application, Dr. Knutson argued that 1α(OH)D4 is "essentially equivalent to 1α(OH)D3 and 1α,25(OH)2D3 in its ability to stimulate an increase in serum calcium." (Declaration Under 37 CFR 1.132 by Joyce Knutson dated August 4, 1994.) Unlike Bishop who provides no data to support his statement at col. 5 to col. 6, Dr. Knutson presents a side-by-side comparison of vitamin D4 and vitamin D3 to support her statement of equivalency. That data is reproduced here in the attached Exhibit A.

The Knutson patent and file history teach that 1α(OH)D4, 1α(OH)D3 and 1α,25(OH)2D3 have essentially the same calcium activity. In view of these teachings, and in view of the structural similarity of the vitamin D analogues, a person of ordinary skill in the art would have expected 1α(OH)D5 to have similar calcium activity. Surprisingly and unexpectedly, it does not.

The Claimed Vitamin D5 Compounds Have Surprisingly Low Calcemic Activity

Applicants have found that 1α(OH)D5 is unexpectedly superior to its vitamin D analogues, including 1α(OH)D4. When applicants synthesized 1α(OH)D5 for the first time, they did not expect 1α(OH)D5 to be significantly different from 1α(OH)D4 and 1α(OH)D3, partly because Knutson taught that the vitamin D analogues should have similar calcium retaining ability, although perhaps different toxicity. To applicants surprise, 1α(OH)D5 resulted in significantly lower calcium levels when administered to rats in controlled tests (see the Declarations of Dr. Robert Moriarty and Dr. Samad Hedayat previously filed).

As evidenced by the Moriarty and Hedayat Declarations, 1α(OH)D5 has substantially lower calcemic activity than 1α(OH)D4 or 1α(OH)D3 at a low to moderate dosage of 0.250 mcg/kg/day (7.9 ± 1.5 versus 11.6 ± 0.45). This difference is so significant that 1α(OH)D5 is believed by applicants to be a much more useful compound in the treatment of certain types of cancer than either 1α(OH)D4 or 1α,25(OH)2D3.

Secondary Considerations - Published Evidence That The Claimed Vitamin D5 Compounds Show Great Promise To Fulfill A Long Felt But Unsolved Need

This difference in effect on serum calcium levels is so significant that 1α(OH)D5 is being considered for therapeutic applications for which 1α(OH)D4 and 1α(OH)D3 are considered unsuitable. Applicants have already placed into the record an article published in the Journal of the National Cancer Institute entitled "Prevention of Prenoplastic Mammary Lesion Development by a Novel Vitamin D Analogue, 1α-Hydroxyvitamin D5", in which the synthesis of 1α(OH)D5 is described and its chemopreventive activity in carcinogen-treated mammary glands is evaluated. The authors of the article (including some of the present inventors) concluded that 1α(OH)D5 is less calcemic than 1α,25(OH)2D3, nontoxic at a range of concentrations, but potent in inhibiting the development of Prenoplastic lesions in mammary glands in organ culture.

In that same issue of the Journal of the National Cancer Institute, an editorial stated that "A major focus of chemopreventive research in the field of vitamin D and cancer has been to synthesize analogues of 1α,25(OH)2D3 that have antiproliferative effects against cancer cells without resulting in hypercalcemia when they are administered in vivo at pharmacological doses." Id. at 183. This editorial indicates a need for improved cancer preventive compounds. Applicants' article in that same issue is clear evidence that 1α(OH)D5 shows

great promise for fulfilling this need.

Because of this great promise, applicants continue conducting research on 1α(OH)D5, funded partially by the National Institutes for Health, and publishing their results. Exhibit B is a reprint of another article recently published in the Journal of the National Cancer Institute entitled "Prevention of N-Methyl-N-Nitrosourea-Induced Mammary Carcenogenesis in Rats by 1α Hydroxyvitamin D5." This article was also written by some of the inventors of the present invention. The article explains that the use of the active form of vitamin D, 1α,25(OH)2D3, in cancer prevention and treatment is limited because it induces excessive blood calcium levels (hypercalcemia). Since the Knutson Declaration teaches that 1α(OH)D4 will induce blood calcium levels "essentially the same as" 1α(OH)D3 and 1α,25(OH)2D3, it follows that 1α(OH)D4 would likewise be unsuitable for cancer prevention and therapy where excessive blood calcium levels is a concern. Had 1α(OH)D5 been found to have calcium activity similar to its vitamin D analogues, it, too, would have been unsuitable for cancer prevention where excessive blood calcium levels are a concern.

However, surprisingly, 1α(OH)D5 has proven to be significantly less calcemic than its vitamin D analogues at low to moderate concentrations, and therefore very promising in the prevention and treatment of breast cancer. Exhibit B is clear evidence that 1α(OH)D5 shows much promise in fulfilling a long

felt but previously unmet need for improved drugs for the prevention and treatment of breast cancer.

The results discussed in Exhibit B involved studies with rats. Studies involving dogs have now been done at IIT Research Institute (IITRI) in Chicago and will soon be reported. This work is summarized in Exhibit C, a copy of an abstract accepted for presentation and publication on the toxicity of vitamin D compounds in rats and dogs, entitled "Preclinical Toxicity of 1α-Hydroxyvitamin D5 In Rats And Dogs." As in the Exhibit B study, the abstract indicates that 1α(OH)D5 has been shown to be a promising compound for prevention and treatment of breast cancer.

The IITRI study was conducted to characterize the toxicity of sub-chronic administration of 1α(OH)D5[1]. It was found that the maximum tolerated dose (MTD) for 1α(OH)D5 is greater than 10μg/kg/day in rats and 5 μg/kg/day in dogs. When compared with published data, these results suggest that the MTD for 1α(OH)D_5 is higher than is the MTD for the active metabolite 1α,25(OH)2D3. This positive result is directly attributable to the surprisingly lower calcemic activity of 1α(OH)D5.

Summary

In side by side tests reported in the Moriarty Declaration, the administration of 1α(OH)D5 at low to moderate dosages

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[1] The IITRI work was carried out under the FDA required Good Laboratory Practice protocols.

resulted in a statistically significantly lower effect on serum calcium than its closest analogues, 1α(OH)D4 and 1α,25(OH)2D3. This window of safety is unique to 1α(OH)D5 and permits its potential use as a human drug. Continuing studies confirm the great promise of 1α(OH)D_5 in the prevention and treatment of cancer, particularly breast cancer.

For the foregoing reasons, applicants submit that Claims 1-6 and 10-19 are in condition for allowance. Applicants request an early and favorable ruling allowing same. The Examiner is invited to telephone applicants' undersigned attorney if any unresolved matters remain.

Respectfully submitted,

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